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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,226	11/22/1999	JACK HENKIN	6356.US.P3	3545

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	20

DATE MAILED: 04/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/447,226	HENKIN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16 and 18-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *12,13,18-32,34-39 and 41-46* is/are allowed.

6)☒ Claim(s) *1-11,14,16,33 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 18 (filed 1/31/03), claims 1, 7, 10, 12, 16, 28-32 have been amended, and claims 33-46 added. Claims 1-14, 16 and 18-46 are pending. Applicants' arguments filed 1/31/03 have been considered and found persuasive in part. The rejection of claims 28-32 under 35 U.S.C. 112, first paragraph is withdrawn. Claims 12, 13, 18-32, 34-39, 41-46 are characterized as allowable.

*

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending application Serial No. 09/833,196, or claim 1 of Serial No. 09/718951 or claim 1 of Serial No. 09/703233. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genus. In each case, the respective genera do not coincide, but there is overlap between the genus of claim 1 of 09/447,226 ~~09/833,196~~ and the genera of claim 1 of each of the cited applications.

[This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As presented in table 2 (page 41), the compound of example 1 is effective to inhibit neovascularization in rat corneas. Also shown (pages 191-192) is that several of the claimed compounds can inhibit microvascular endothelial migration *in vitro*. It is stipulated that inhibition of angiogenesis will occur both *in vitro* and *in vivo*. But applicants are extrapolating from these *in vitro* results to treatment of various diseases such as cancer, arthritis, pathological angiogenesis resulting from infection, macular degeneration, and diabetic retinopathy. Perhaps it is true that under carefully controlled laboratory conditions, using a certain species of rat, and using a specific tumor cell line, some reduction of tumor volumes has been observed using one or two compounds other than those claimed. However, structure/function relationships are "unpredictable" where angiogenesis is concerned, i.e., inhibition of angiogenesis is a question of degree. As stated in *Ex parte Forman* (230 USPQ 546, 1986). and subsequently affirmed in *In re Wands* (8 USPQ2d

1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

It is stipulated that inhibition of angiogenesis will occur in vivo, and that inhibition of tumor cell proliferation will also occur *in vivo*. However, such inhibition is not necessarily predictive of therapeutic success. If the degree of inhibition is insufficient, an improvement in the patient's condition will not be realized. In addition, there is the matter of bioavailability/pharmacokinetics, and xenobiotic metabolism. These paramaters will all change (in unpredictable ways) with structure of the compounds. Consider also the following:

- Nicosia (*American Journal of Pathology* **138** (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* **25** (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke, "Tissue examination to monitor antiangiogenic therapy: a phase I clinical trial with endostatin" (*Clinical Cancer Research* **7** (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor. The result is that the endostatin was not particularly effective in treating cancer

patients.

- Pignatelli (*Human Pathology* **23** (10) 1159-66, 1992) discloses that in breast carcinomas, expression of integrins is downregulated. This tends to suggest that if one makes "static" assumptions about the level of expression of integrins on tumor cells, an "unpredictable" outcome is likely.

Thus, one can conclude even if angiogenesis can be achieved by a given compound "X", reduction of tumor volumes by the compound "X" is "unpredictable".

In accordance with the following, "undue experimentation" would be required to practice those embodiments wherein therapeutic efficacy is concerned.

In response to the foregoing, applicants have argued that (a) the claimed compounds inhibit metastasis; (b) the claimed compounds inhibit angiogenesis; (c) the claimed compounds inhibit neovascularization; and (d) the claimed compounds inhibit proliferation of tumor cells. While each of these conclusions may be valid, none supports the contention that therapeutic efficacy can be realized in the treatment of humans (or other mammals) afflicted with cancer. If cancer cells in a human are proliferating at the rate of 100 "units" per day in the absence of the compound, and only 90 "units" per day in the presence of the compound, one can say that inhibition had occurred. But if the cancer cells are still proliferating (even if at a slower rate), the patient's condition will only worsen, and one cannot say that a successful treatment had been realized. In addition, applicants have

pointed to Reiher (*Int J. Cancer* **98**, 682, 2002). Reiher discloses that the following compound exhibits some degree of antitumor efficacy in mice:

Ac-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-NHEt.

However, this compound falls outside the scope of claim 1 (and all claims that are properly subgeneric thereto).

Accordingly, it remains that enablement is lacking for each of claims 14 and 16.

*

Claims 1-11, 14, 16, 33, 40 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, it is recited that variable "A_4" can be D-glycine, or L-glycine. However, glycine is not a chiral molecule; designations of chirality are thus moot. The same issue (with respect to glycine) applies in the case of variables A_5, A_6 and A_7.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600